

Improving Resectability of Hepatic Colorectal Metastases: Expert Consensus Statement By Abdalla et al.

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Treatment of colorectal metastatic disease has changed dramatically over the past 10 years. Liver resection has been the only accepted curative treatment option for patients with metastatic colon cancer, but the introduction of better imaging, newer ablative techniques, improved systemic therapies and improved patient selection has increased the number of patients eligible for consideration for this goal. To date, there have been only modest prospective clinical trial efforts in this population to evaluate long-term benefits in relapse-free and overall survival, as well as, in patients who have undergone resection. This consensus conference is timely in bringing together leaders in the field in an effort to consolidate current approaches to this disease. This effort is laudable, focusing the discussion on the current standards for care of colorectal liver metastases (CLM), while highlighting the areas of controversy and the unanswered questions. Like all good academic endeavors, it raises as many questions as it answers.

CHEMOTHERAPY AND UNRESECTABLE COLORECTAL LIVER METASTASES

Chemotherapeutic advances have led the way for many of the improvements in treating CLM. In addition to the patients whose metastases are initially resectable, there appears to be a small, but defined, group of patients in whom disease appears to be unresectable, based on a number of factors such as size, number and location, in whom perioperative therapy allows for consideration of ablative therapies. By consensus, for patients with disease isolated to the liver that is initially anatomically unresectable, preoperative chemotherapy is recommended.

Rene Adam and the group from Hôpital Paul Brousse have steadily advanced the use of preoperative chemotherapy as a means of downsizing CLM to allow resection.¹ The data are convincing that a large minority of technically unresectable metastases (20%) become resectable by this approach. Long term survival is substantial (33%, 5-year survival) but does not yet reach the 58% survival rate from recent reports.² As systemic therapy continues to improve, it is reasonable to expect that CLM in additional patients will be rendered resectable, with more long-term survivors.

This approach does raise a multitude of new questions and issues. One issue surrounds the emerging data that systemic therapy injures the liver, potentially to the point of retarding regeneration and function, leading to an increase in morbidity and mortality.³ How do we account for this in our treatment strategy? Does chemotherapy need to be stopped before hepatic resection to allow a period of hepatic recovery? If so, how long before resection? In

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particular, for bevacizumab, which has been associated with bleeding/healing complications, do we need to stop it earlier (8 weeks), as has been suggested by some? Hepatic injury appears to be related to the duration of systemic therapy, some reports suggesting as little as 8–12 weeks, resulting in observable hepatic changes. If this is the case, how do we account for this in our practice? If a longer duration of systemic therapy is required to achieve resectability, how do we assess the status of the FLR? Currently, no functional tests appear to be predictive. Likewise, biopsy of the FLR does not appear to be helpful in predicting postoperative hepatic function. Thus, should all patients receiving the threshold amount (whatever that is) of chemotherapy be considered for portal vein embolization (PVE)? Despite these concerns, Adam et al. treated patients with a mean of ten cycles of systemic therapy, reporting excellent results without the routine use of PVE. Again, these questions are pertinent to our daily practice but remain unresolved.

Another issue includes patients who respond well to systemic therapy with a substantial reduction in the size of their metastatic lesions. Many authors have advocated resection as soon as the lesions are technically operable. However, in practice, many oncologists' inclination is to continue systemic therapy to "maximal benefit". This has resulted in a population of patients with very small residual nodules apparent by cross-sectional imaging but negative on positron emission tomography (PET). Some have advocated resection of these residual nodules, others a watch and wait strategy to determine whether they contain active tumor (growth over time). The appropriate approach remains to be elucidated. Also troublesome are patients with complete resolution of their CLM with systemic therapy. Adam et al.⁴ have advocated resection of the liver based on pre-treatment localization, presenting data that indicate that >90% of these patients have residual tumor detectable on pathologic examination despite a radiological complete or near complete response. However, this situation also raises the question as to whether close observation, followed by resection of areas demonstrating active tumor on follow-up, would result in smaller parenchymal resections or potentially avoid resection altogether in those patients without active tumor. Finally, this approach is difficult to apply in patients with multi-focal bilobar disease in which enough of the lesions disappear to render the patient technically resectable. Resecting the remaining involved parenchyma, as well as parenchyma previously involved, is not feasible, due to the lack of a

sufficient FLR. Again, the best approach in these circumstances is unknown.

PORTAL VEIN EMBOLIZATION

Our understanding of liver volumes and their relationship to postoperative liver function and the technical improvements in PVE have progressed substantially over the past 5 years. It is clear that not all livers are created equal; segmental volume is substantially different between individuals. The prudent course, based on the current data, involves volumetry of the FLR when resection of more than four segments is anticipated. PVE clearly works to increase hepatic volume.^{5,6} Less clear is its application in specific circumstances. While general volume guidelines have been offered, the critical missing piece is a function test linked to the FLR. Currently, none are available. Until function assessment becomes reality, it will be difficult to sharpen the distinction between an adequate FLR and one that has too much steatosis, venous congestion, fibrosis, or cirrhosis to support adequate recovery after resection. While some authors have cautioned against the overuse of PVE, its use in marginal FLR cases should be strongly considered. In experienced hands, there appears to be relatively little downside.⁷

ABLATION OF UNRESECTABLE DISEASE

It is important to reemphasize in this section that hepatic resection is the primary treatment for CLM and the only curative modality currently available. Radiofrequency ablation (RFA) is not a substitute for resection, based on currently available data. Following FDA approval, Pandora's box has been opened; nearly every sizable institution now has ablation technology. As a result, it is being offered in the absence of a multidisciplinary approach for the treatment of these patients. More concerning, RFA is being offered as first line, equivalent therapy for patients with resectable disease. The data presented here and elsewhere do not support this practice.² As a result, it should not be considered standard care and its use in this context should be discouraged in the absence of new data indicating otherwise.

Patients with a FLR predicted to be inadequate following resection, who have an inadequate hepatic reserve to tolerate resection or are medically unfit for operation, are potential candidates for ablative therapies. In our experience, few, if any, medically fit

patients with normal liver function and CLM fall into this category. Patients with normal livers and technically unresectable CLM typically are not ablation candidates for the same reason they cannot undergo R0 resections, including tumor size, multifocal disease, ill-placed tumors, or proximity to major vascular or biliary structures. Practically speaking, ablation for CLM in this situation is most useful for patients with bilobar disease undergoing resection combined with ablation or for patients with prior extensive or multiple resections who would have an insufficient FLR to allow further resection.

At present, the utility of ablation for CLM is limited to those patients unable to tolerate curative resection. However, with improvements in targeting technology and real-time ablation assessment, treatment of small lesions (<3 cm) may well become feasible and a reliable alternative for patients with oligo-metastases.

RESECTION OF EXTRAHEPATIC DISEASE

Improved experience with resection, coupled with better systemic agents, has led to long-term survival following resection of extrahepatic colorectal metastases. This is particularly true for pulmonary metastases and organs (diaphragm, colon, or stomach) involved by direct extension. Current data support aggressive resection for individuals with these presentations.

Pushing the limits as an extension of this concept are reports supporting resection of lymph node metastases, particularly in the hepatoduodenal lymph nodes or for limited peritoneal disease. Current data suggest lymph node disease limited to the hepatoduodenal ligament may negatively impact prognosis but does not preclude long-term survival in all cases.⁸ However, these data are too immature to endorse resection as routine policy. Additional data from other centers are needed to enable us to understand the role of resection in these patients. Again, as systemic therapy improves, the impact on survival of lymph node involvement in these areas is likely to decrease. These findings raise some interesting questions. Should we do lymph node sampling prior to resection in these areas? If so, when; routine lymph node sampling, only when the nodes are clinically involved, or guided by the prognostic factors found to be associated with increased lymph node involvement? If you choose to sample, would a positive lymph node in area 1 preclude resection in a low risk patient? Currently, since these questions remain

unanswered, routine lymph node sampling or resection does not appear to be supported by the literature.

The role of resection for peritoneal carcinomatosis, including limited disease, is even less clear. While several small studies report encouraging results with peritoneal debulking and intraperitoneal chemotherapy, the benefit of this approach is unproven.⁹ As such, it cannot be considered standard therapy and should be offered only in the form of a clinical trial. Use outside this construct will limit our ability to demonstrate its role in this disease process.

In conclusion, resection is in the eyes of the beholder; in other words, experience counts. If a patient is to be denied a potentially curative hepatic resection for CLM, this assessment should come from an experienced hepatobiliary surgeon working in the context of a multidisciplinary group. Care in this context will allow patients to benefit from the full range of options as outlined in this consensus conference.

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